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ORIGINAL ARTICLE

Role of magnetic resonance spectroscopy in differentiation between recurrence of glioma and post radiation injury



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KEYWORDS

Magnetic resonance spectroscopy;
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Abstract *Purpose:* This study aims to evaluate the role of MR spectroscopy in the detection of recurrent glioma and differentiation from post radiation injury.

Patients and methods: 32 patients (20 males and 12 females) complaining of different neurological symptoms were enrolled prospectively in this study between September 2011 and December 2013. These patients were selected on the basis that they were known patients with pathologically proved glioma who underwent radiotherapy. All patients underwent standard MRI examination and MR spectroscopy.

Results: This study included 32 patients, twenty four patients (75%) proved histologically to be of recurrent glioma (group I) and 8 cases (25%) diagnosed as post radiation injury (group II). Peri-tumoral infiltration was present in 18 cases (56.25%) of recurrent glioma. Significantly increased Cho/Cr and Cho/NAA ratios were observed in neoplastic ($n = 24$) compared with non-neoplastic lesions ($n = 8$). Presence of lactate and lipid yielded correct classification as neoplastic and non-neoplastic lesions.

Conclusion: Magnetic resonance spectroscopy is a useful tool for the detection of recurrent glioma and differentiation from post radiation injury.

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1. Introduction

Distinguishing between radiation necrosis and tumoral recurrence represents a difficult diagnostic challenge. Radionecrosis at tumor bed may mimic recurrent glioma, while any radiation-induced lesions detected distant to the primary tumor site may be misinterpreted as multifocal glioma (1).

Table 1 Histopathological diagnosis of 32 patients suspected of recurrent glioma.

Final diagnosis	No. of patients	%
Recurrent glioma (group I)	24	75
-Glioblastoma multiformis	16	
-Anaplastic astrocytoma	7	
-Low grade glioma	1	
Post radiation injury (group II)	8	25
Total	32	100

Increasingly aggressive radiation treatment protocols are being used in the hope of improving patient survival rates. These regimens can lead to overlap between effective and neurotoxic doses of radiation (2).

MR spectroscopy is providing biochemical information about proliferative tumor activity and has been proposed as

alternative modality for differentiating recurrent tumor from radiation injury (3,4).

Magnetic resonance spectroscopy (MRS) can be used to serially monitor biochemical changes in tumors, stroke, epilepsy, metabolic disorders, infections, and neurodegenerative diseases. To get an accurate assessment of the tumor chemistry, avoiding areas of necrosis, hemorrhage, calcification, cysts or bone is mandatory (5,6).

MR spectroscopy can be performed within 8–10 min and can be added on to conventional MR imaging protocols (7).

2. Aim of the work

The aim of the work is to evaluate the role of MR spectroscopy in the detection of recurrent glioma and differentiation from post radiation injury in the whole area of signal alteration within irradiated region.

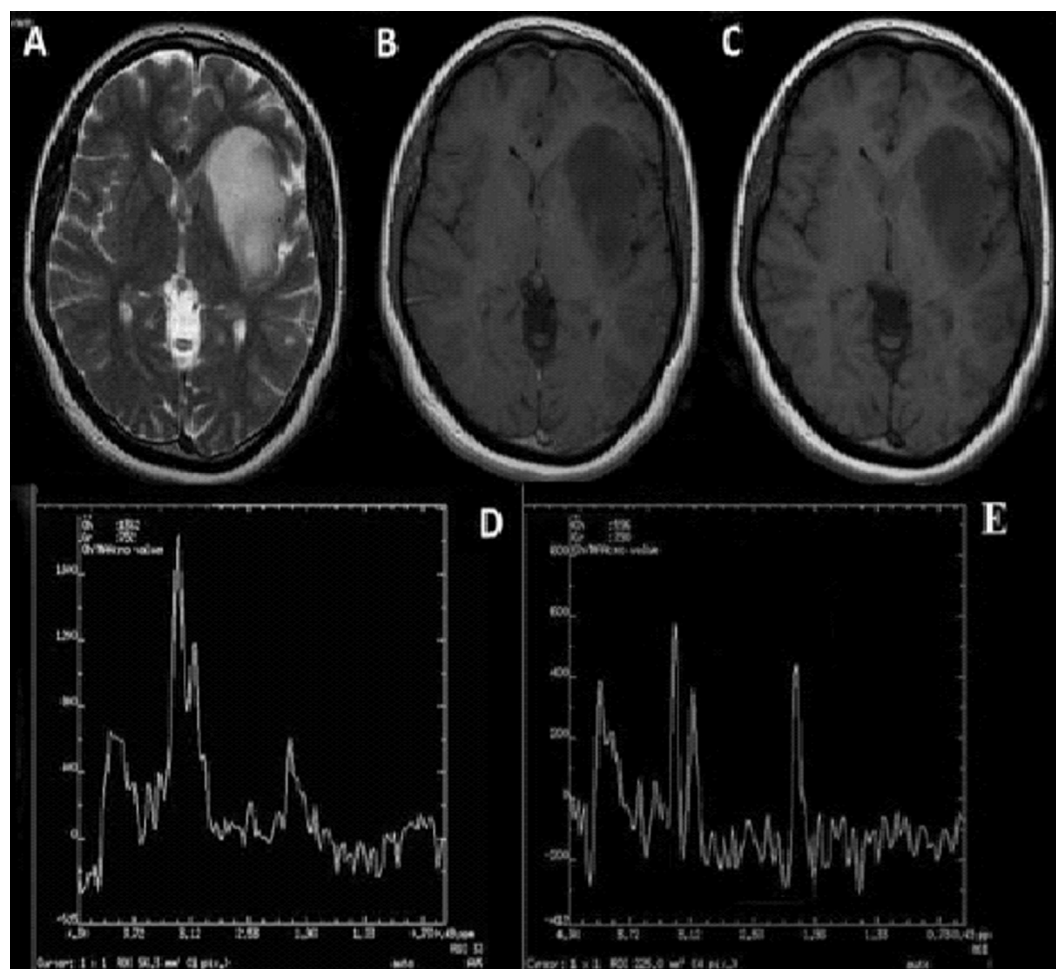


Fig. 1 Recurrent glioma. A fifty year old female with a history of left temporoparietal space occupying lesion, proved by biopsy to be of low grade astrocytoma managed by radiotherapy. After one year she presented with severe headache with vomiting and right hemiparesis. (A) Axial T2 WI of the brain revealed abnormal hyperintense signal intensity at the left temporo-parietal region with mild peri-focal edema. (B) Axial T1 WI of the brain revealed abnormal hypo intense signal intensity at the left temporo-parietal region with mass effect. (C) Post contrast T1 WI of the brain showed no significant enhancement of the previously noted lesion. (D) MRS done with long TE and single voxel technique showing increased Cho peak and decreased Cr and NAA peaks with elevated Cho/NAA ratio (2.2) and elevated Cho/Cr ratio (1.9) with, prominent lactate doublet and no significant increase in lipid peak. (E) Peri-lesional MRS using long TE revealed Cho/Cr ratio about 1.3, suggesting no infiltration in the peri-lesional area.

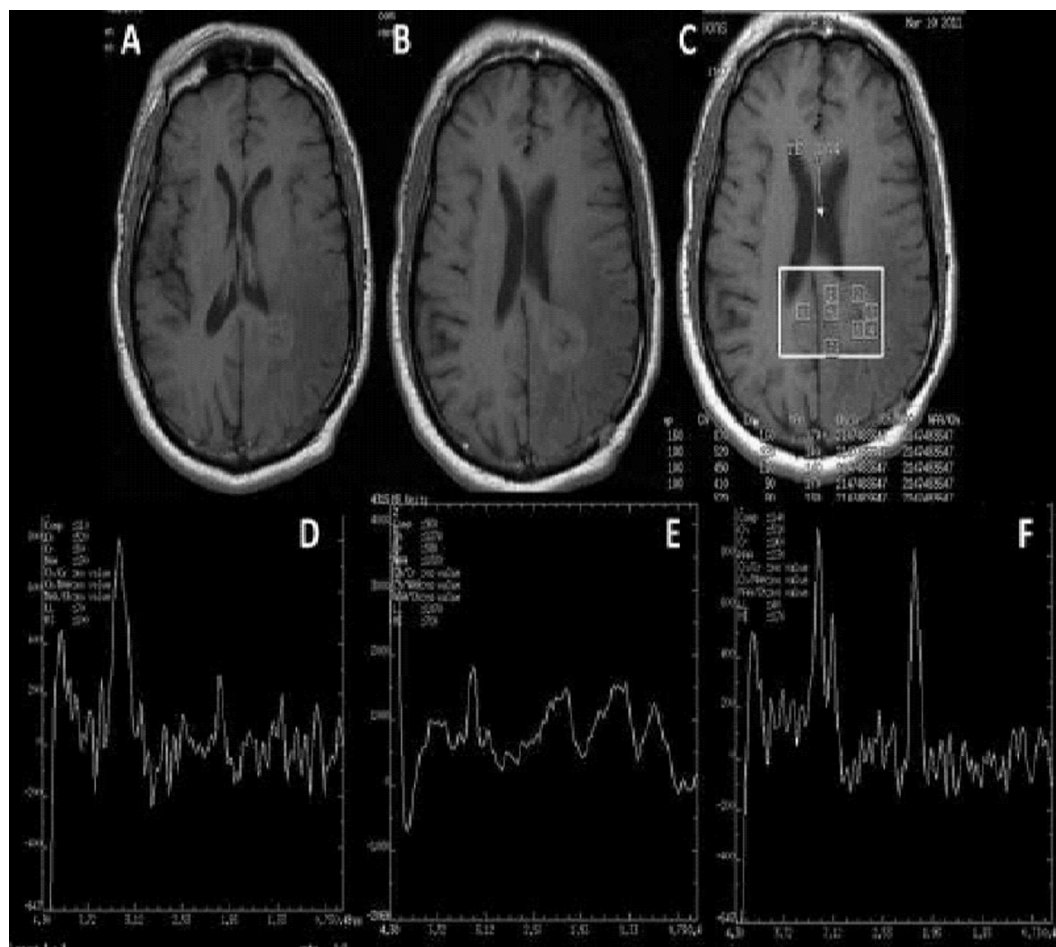


Fig. 2 Recurrent glioma. A fifty year old male with a history of left parieto-occipital anaplastic astrocytoma managed by surgical resection and radiotherapy. One year later he presented with headache and right sided weakness. (A and B) Post contrast axial T1 WI showing heterogeneously enhancing lesion seen at the left occipito-parietal region with mass effect in the form of slightly effaced related cortical sulci. (C) Voxel localization. (D and E) MRS was done with long and short TE using multi-voxel technique and reveals markedly elevated Cho and decreased both Cr and NAA peaks and increased Cho/NAA ratio (4) and markedly increased Cho/Cr ratio (6.5) with mildly elevated lactate peak and mild increase in the lipid peak is also noted. (F) Peri-lesional voxels using long TE showed Cho/Cr ratio 3.1, denoting infiltration.

3. Patients and methods

This prospective study includes 32 patients with the history of previously treated brain tumors, 20 males and 12 females (age range 23–65 years; mean age, 44 years). All patients included in this study received radiation therapy. All patients came to our institute in the period between September 2011 and December 2013, presented with different neurological symptoms. In 18 patients histopathology was available through surgical removal of tumor while stereotactic biopsy was done in 14 patients. Histological findings revealed 24 patients with recurrent glioma (group I) including 16 patients with glioblastoma multiformis, one patient with low grade glioma and 7 patients with anaplastic astrocytoma. Eight patients proved to have post radiation changes (group II). The interval between radiation therapy and MRS ranged between 5 and 11 months. On follow up MRI, the area of signal alteration at or near the site of original tumor within the previously irradiated area was examined by MR spectroscopy. The study was

approved by the local ethics committee at our institution and informed consents were obtained from all patients.

4. Methods

4.1. MRI examination of brain

All the patients were evaluated by standard brain MRI protocol at our institution using a 1.5T. MRI machine (GE Signa 1.5T, GEMSOW), the protocol includes a 3 plane localizer, Axial & Sagittal T1WI, Axial T2 WI, and Axial fluid attenuation inversion recovery (FLAIR). Post contrast T1WI in axial, coronal and sagittal planes using Gadolinium-DTPA (0.2 mg/kg) was done. A slice thickness of 5 and 4 mm spacing was used.

Point resolved spectroscopy (PRESS) technique was applied using the long and short TE (144 and 35 ms) respectively. Sampling analysis was performed by the Multi voxel MR spectroscopic technique (MVS) in all patients, 2 or 3 were

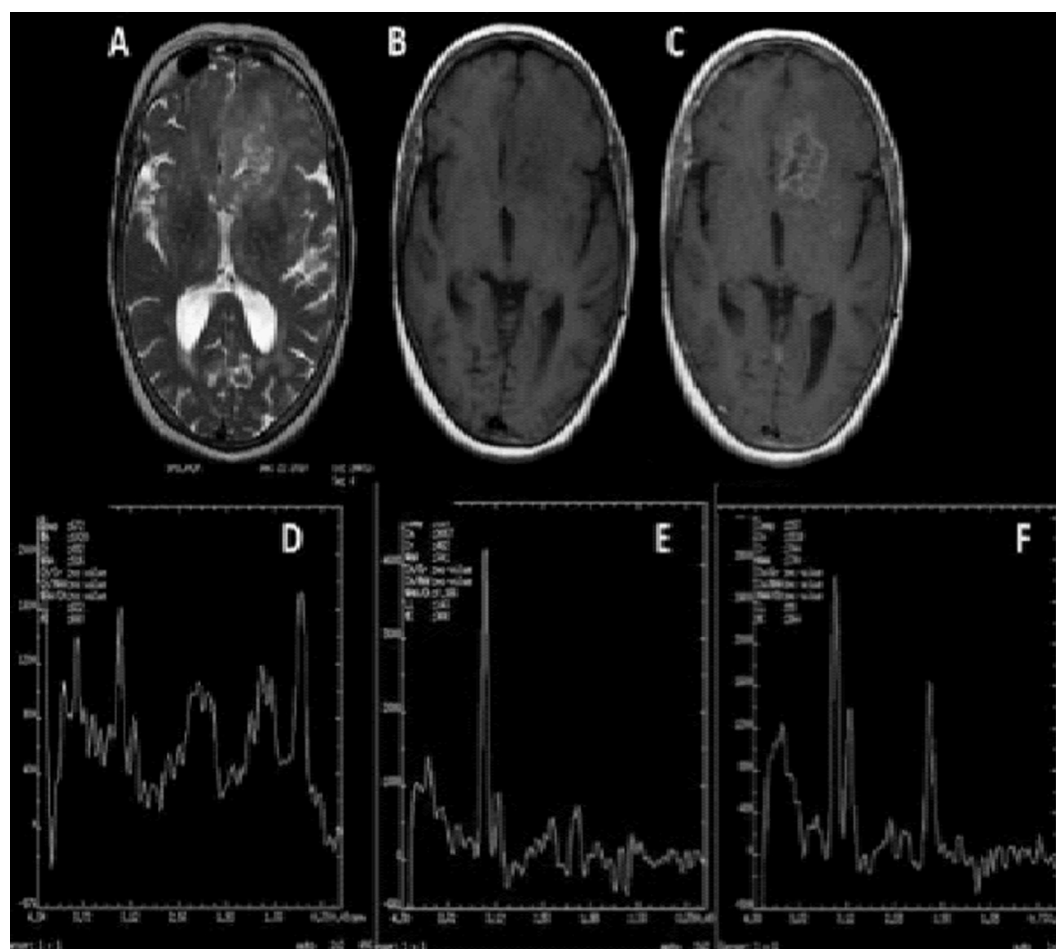


Fig. 3 Recurrent glioma. A sixty-five year old female with a history of left frontal glioblastoma multiformis managed by surgical resection and radiotherapy. Seven months later she presented with severe headache, vomiting and right hemi-paresis. (A) Axial T2 WI showing abnormal heterogenous signal intensity seen at the left frontal region with surrounding mild peri-focal edema and causing mass effect. (B) Axial T1 WI showing hypointense signal in the left frontal region. (C) Post-contrast axial T1 WI showing heterogeneous enhancement of the previously noted lesion. (D and E) MRS was done with short and long TE and reveals markedly elevated Cho and decreased both Cr and NAA peaks and elevated Cho/NAA ratio (6) and increased Cho/Cr ratio (4.4) with elevated lactate peak and an increase in the lipid peak is also noted. (F) Peri-lesional MRS using long TE revealed elevated Cho/Cr ratio (2.1), denoting infiltration.

positioned in the solid parts of the lesions guided by enhancement in post contrast T1WIs avoiding areas that showed signs of hemorrhage or necrosis, also avoiding contamination from nearby bone or CSF spaces, the voxel size ranged from $1 \times 1 \times 1 \text{ cm}^3$ to $2 \times 2 \times 2 \text{ cm}^3$, other similar voxels (2 or 3) were placed in peri lesional edema. A voxel was positioned in the contralateral normal brain white matter to obtain a reference spectrum. Choline/Creatine and Choline/N-Acetyl Aspartate ratios were calculated for the tumor and peri tumoral edema. Lipid and lactate peaks were read at 1.3 ppm on long and short TE sequences as present or absent. Surgical resection was performed in 18 patients and stereotactic biopsy in 14 patients, the resected specimens were evaluated by histopathology.

Statistical analysis was performed using the Mann–Whitney *U* test to compare MRS ratios in recurrent glioma and post radiation necrosis, Chi-square test was performed on the lipid peak in long and short TE, *p* value of <0.05 was considered statistically significant. Software used was Minitab V.17 (Minitab Inc. USA).

5. Results

Depending upon histopathological examination (Table 1) 24 cases (75%) were found to be of recurrent glioma (group I) and 8 cases (25%) diagnosed as post radiation injury (group II).

On T1-weighted images with Gadolinium DTPA (Gd-DTPA), 31 cases showed variable contrast enhanced lesions while one case of low grade glioma had no area of contrast enhancement (case 1).

MR spectroscopy revealed 25 patients with pathological spectra of recurrent/residual tumors, 24 patients with enhancing lesions (case 2 and 3) while one revealed no enhancement within lesional area at intralesional voxels (Case 1). In eighteen of these cases, MR spectroscopy revealed perilesional infiltration in voxels outside the area of enhancement (case 2 and 3). The case presented with no enhancement within the lesion on Gd-DTPA enhancing images elicited spectra characteristic for tumor (case 1) with no perilesional infiltration. This

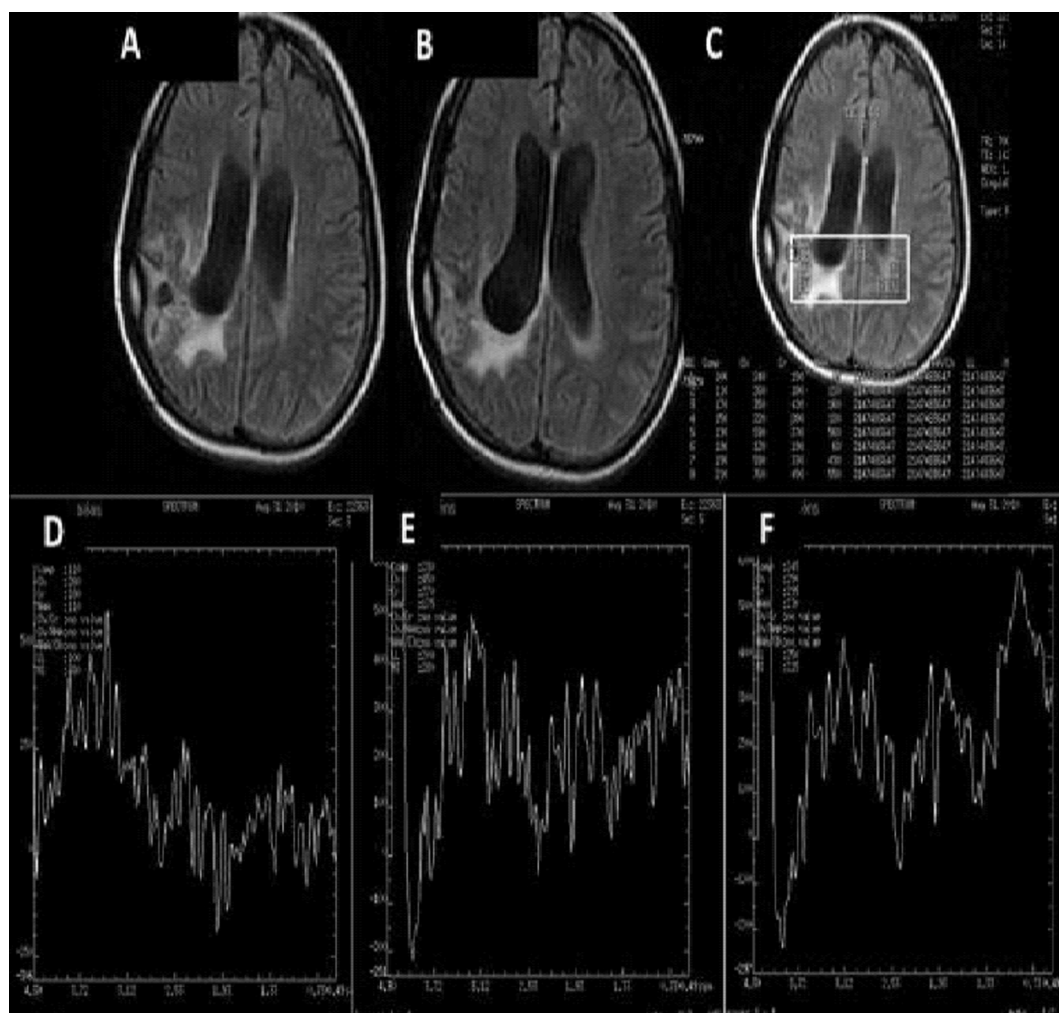


Fig. 4 Post radiation injury. A thirty-eight year old male with a history of right parieto-occipital glioma managed by surgical resection and radiotherapy. Nine months later he presented with severe headache. (A and B) Axial FLAIR WIs showing abnormal heterogeneous signal intensity seen at the right parieto-occipital region with mild peri-focal edema and negative mass effect upon the related right lateral ventricle. (C) Voxel localization. (D and E) Intra-lesional MRS using long (left image) and short TE and multi-voxel technique showing elevated Cho peak with decreased Cr and NAA peaks and increased Cho/NAA ratio (2.36) and increased Cho/Cr ratio (1.6) and increased lipid peak at 0.8 ppm with prominent lactate peak. (F) Peri-lesional voxels using short TE showing Cho/Cr ratio 0.98, suggesting no infiltration in the peri-lesional area as well.

allowed better delineation of tumor margin and extent. Pathological MR spectra characteristic for recurrent/residual tumor revealed a highly elevated Choline peak ($n = 22$), marked depressed NAA ($n = 23$) and elevated lipid/lactate peaks ($n = 12$). Pathological spectra denoting post radiation injury (7 cases) carry the following criteria; mild elevated choline peak, mild depressed NAA peak and slight elevation of lipid/lactate peaks (Figs. 1–5).

The values of Cho/Cr ratio of the lesional area were lower in post radiation injury (1.37 ± 0.30) than recurrent gliomas (4.41 ± 0.65) (Table 2). A statistically significant difference was seen between intralesional Cho/Cr ratio values in post radiation injury versus recurrent gliomas with $p = 0.0003$ and $p = 0.019$ respectively. Cho/Cr ratio of the perilesional area was higher in recurrent gliomas (2.213 ± 0.85) than post radiation injury (1.267 ± 0.333). Perilesional infiltration was detected in 18 patients out of 24 patients in group I (case 2 and 3). No peritumoral infiltration could be detected at cases

of post radiation injury (cases 4 and 5). A statistically significant difference was seen between Cho/Cr ratio values in post radiation injury versus recurrent glioma with $p = 0.0225$ and $p = 0.0139$ respectively (Table 2).

The values of Cho/NAA ratio of the suspected lesional area were lower in post radiation injury (1.89 ± 0.30) than recurrent gliomas (7.466 ± 1.16) (Table 3). A statistically significant difference was seen between the values of Cho/NAA ratio in post radiation injury versus recurrent gliomas with $p = 0.0003$ and $p = 0.019$ respectively. Cho/NAA ratio of the perilesional area was higher in recurrent gliomas (2.855 ± 0.92) than post radiation injury (1.19 ± 0.17). Perilesional infiltration was detected in 18 patients out of 24 patients in group I. A statistically significant difference was seen between Cho/NAA ratio values as shown in Table 3.

Both long and short TE (144 and 35 ms) respectively were used to evaluate the presence of lactate and lipid. The lactate peak was well demonstrated on long TE while the lipid peak

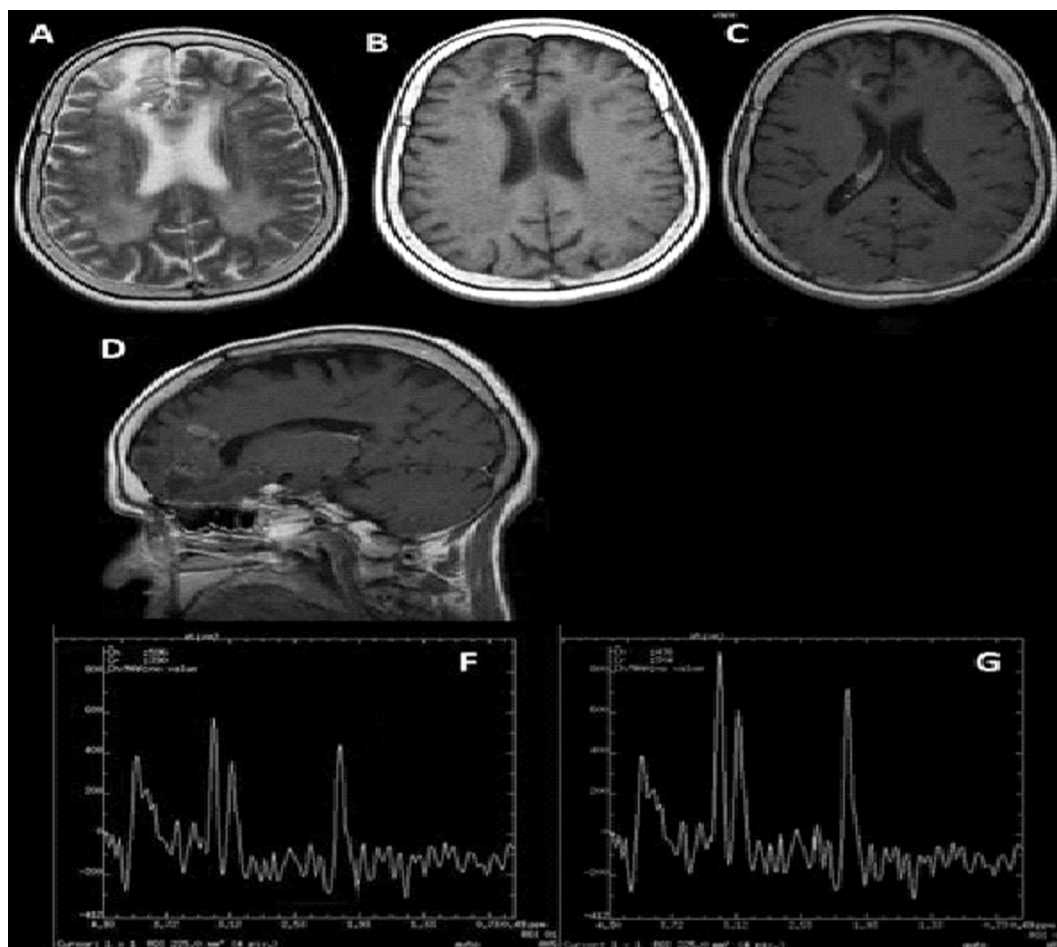


Fig. 5 Post radiation injury. A forty-five year old female with a history of right frontal astrocytoma managed by radiotherapy. Eight months later she presented with severe headache. (A) Axial T2 WI showing heterogeneous hyperintense signal in the right frontal region, surrounded by mild peri-focal edema. (B) Axial T1 WI showing hypointense signal in the right frontal region. (C) Post-contrast axial T1 WI showing mild enhancement of the previously noted lesion. (D) Post-contrast sagittal T1 WI showed the enhancement of the lesion. (E) Intra-lesional MRS using long TE and single voxel technique showed elevated Cho peak with slightly decreased NAA and Cr peaks and elevated Cho/NAA ratio (1.9) and mildly increased Cho/Cr ratio (1.4) with no significant increase in either lactate or lipid peaks. (F) Peri-lesional MRS using long TE revealed Cho/Cr ratio about 1.4, suggesting no infiltration in the peri-lesional area as well.

Table 2 Showing Cho/Cr ratios in lesional and perilesional regions of the cases on long TE (144 ms).

	Recurrent glioma	Post radiation injury
Cho/Cr intralesional	4.41 ± 0.65	1.37 ± 0.30
Cho/Cr perilesional	2.213 ± 0.85	1.267 ± 0.333

Table 3 Showing Cho/NAA ratios in lesional and perilesional regions of the cases on long TE (144 ms).

	Recurrent glioma	Post radiation injury
Cho/NAA intralesional	7.466 ± 1.16	1.89 ± 0.30
Cho/NAA perilesional	2.855 ± 0.92	1.19 ± 0.17

was much more evident on short TE. Chi square test showed a statistically significant difference between the presence of lipid peak in recurrent glioma and post radiation injury on both long and short TE $p = 0.02$ and $p = 0.47$ respectively.

On long TE (144 ms), lactate peak alone was seen in 12 cases including 10 recurrent glioma and 2 post radiation necrosis (Table 4) while combined existence of Lip./Lact was seen in 5 cases including 4 cases of recurrent glioma and one case of post radiation. Lipid peak alone was seen in 13 cases including 8 recurrent glioma and 5 post radiation necrosis. Lactate peak was less evident on short TE (35 ms) (Table 5).

Table 4 Showing lipid and lactate peaks on long TE 144 ms.

	Lipid	Lip./Lact	Lactate	None
Recurrent glioma	8	4	10	2
Post radiation injury	5	1	2	—

Twenty-four of the 25 patients diagnosed on MRS as recurrent/residual tumor proved to be correctly diagnosed on comparison with the histopathological study. Only one lesion was

Table 5 Showing lipid and lactate peaks on short TE 35 ms.

	Lipid	Lip./Lact	Lactate	None
Recurrent glioma	14	7	1	2
Post radiation injury	6	2	–	–

diagnosed on MRS as tumor and proved to be post radiation injury on histopathology. The combination of Cho/Cr and Cho/NAA ratios resulted in sensitivity = 100%, specificity = 88.8%, accuracy = 96.6%, PPV = 96% and NPV = 100%.

6. Discussion

Among the non invasive methods that are available for diagnosing intracranial tumors, MRS has been used in attempts to differentiate tumor from radiation necrosis (8).

However the study of Weybright et al. (8) and Rock et al. (9) revealed that the ability of MRS in detecting tumor was seen not only in the contrast-enhancing regions but also, even more important, outside this area in 38% of patients with recurrent tumor. This ability of multi voxel spectroscopic imaging to detect tumor tissue outside the area of contrast enhancement in the same acquisition leads to an increase in the chance of discovering tumor recurrence and also change the options for further treatment, this is matching with the present study as 18 patients (75%) out of 24 patients in group I have peri-lesional infiltration.

This study showed statistically significant difference between intralesional Cho/Cr ratio values in post radiation injury versus recurrent gliomas with $p = 0.0003$ and $p = 0.019$ respectively. This is in agreement with Zeng et al. (10) who found that Cho/Cr ratios are significantly higher in recurrent tumors than in radiation injury.

The current study revealed a statistically significant difference between intralesional and perilesional Cho/Cr ratio values in post radiation injury versus recurrent gliomas and this is in agreement with Smith et al. (11) and Server et al. (12) who developed a method using alterations in ratios of standard brain metabolites-choline (Cho), creatine (Cr), and N-acetylaspartate (NAA)-to predict the probability of tumor recurrence in patients previously treated for brain tumors and developing new contrast-enhancing lesions. Elevations of metabolic ratios Cho/Cr were found in patients with recurrent tumor more than those with post-radiation change.

Narayana et al. (13) used Cho/Cr ratio as a marker for tumor definition. In the present study Cho/NAA ratio was able to discriminate between recurrent/residual tumor and radiation injury. Large prospective studies in the future using sophisticated prediction models, new methods like 3D MRS, and target-guided biopsies with histologic confirmation are needed to reach a consensus about the true value of MRS as a method of differentiating recurrent/residual tumor from radiation injury as told by Sundgren (14). The 3D MRS technique provides full lesion coverage, higher spatial resolution, as well as including surrounding and contralateral brain regions as stated by Horská (15).

Lipid peaks were seen in recurrent glioma on both long TE (144 ms) and short TE (35 ms) sequences however the peaks

were higher on short TE sequences. A statistically significant difference between the presence of a Lipid peak between recurrent gliomas and post radiation injury on both short and long TE sequences was seen. This agreed with Shokry (16), Opstad et al. (17) and van der Graaf (18) who stated that lipid peaks are detected at recurrent glioma on short and long TE with a statistically significant difference between the presence of a Lipid peak between recurrent gliomas and post radiation injury on both short and long TE sequences was seen.

Lactate peak was seen on long TE sequences (TE 144) in 10 cases of recurrent glioma and 2 cases of post radiation injury. Law et al. (19) reported the presence of lipids and lactate peaks in recurrent glioma. Lipid and lactate presence correlates with necrosis in post radiation injury (19).

The limitation and recommendation of this study:

- Long term follow up is needed as well as statistical analysis of sample in the form of survival analysis.

In conclusion, Multi-voxel Magnetic resonance spectroscopy is useful in the evaluation of recurrence of glioma, also allows better delineation of tumor margin and extent and differentiation between the recurrent glioma and post-radiation injury.

Conflict of interest

None.

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